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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/805,650	03/19/2004	Michael Borns	25436/2382	9645

27495 7590 08/17/2007

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EXAMINER
STAPLES, MARK

ART UNIT	PAPER NUMBER
1637	

MAIL DATE	DELIVERY MODE
08/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/805,650	BORNS, MICHAEL	
	Examiner	Art Unit	
	Mark Staples	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *12,14,16-18,20-24 and 31-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13,15,19,25-30 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' amendment of claims 1-5, 7, 9, 11, 13, 15, 16,19, 20, 25-27, 30, 31-32, and 34-38 and submission of new claim 40 in the paper filed on 06/08/2007 is acknowledged. Per the previous Office Action claims 1-11, 13, 15, 19, 25-30 are the previously elected claims.

Claims 1-11, 13, 15, 19, 25-30, and 40 are pending and at issue.

2. Applicants' arguments filed on 06/08/2007 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Objections and Rejections that are Withdrawn

3. It is acknowledged that Applicant has amended the specification for proper use of the trademark VENT®. However the trademark DEEP VENT® needs to capitalized as well.

Claim Objections Withdrawn

4. The objections to claims 3, 7, and 9 are withdrawn in light of Applicant's amendment of these claims to overcome the objections.

Claim Rejections Withdrawn - 35 USC § 112 First Paragraph

5. The rejections of claims 7 and 9 under 35 USC § 112 First Paragraph for recitation of "under proper conditions" are withdrawn.

Applicant's arguments, see p. 15, filed 06/08/2007, with respect to claims 7 and 9 have been fully considered and are persuasive. The rejection of claims 7 and 9 has been withdrawn.

6. The remaining rejections of claims 1-11, 13, 15-16, 19-20, and 25-30 under 35 USC § 112 First Paragraph are withdrawn in light of the Applicant's amendment of these claims to overcome these rejections.

Claim Rejections Withdrawn - 35 USC § 112 First Paragraph

7. The rejections of claims 1-11, 13, 15, 19, and 25-30 under 35 USC § 112 First Paragraph are withdrawn in light of the Applicant's amendment to limit the scope of claims 1, 3, 5, and 7 to limit the scope to the disclosed DNA polymerase fusion which comprises wild type *Pyrococcus furiosus* polymerase I fused to *Sulfolobus solfataricus* SSso7d protein.

Claim Rejections Withdrawn - 35 USC § 102(b)

8. The rejection of claims 1-4, 7-11, 13, 15, 19, and 25-30 under 35 USC § 102(b) as being anticipated by Wang (2001) are withdrawn.

Applicant's arguments with respect to claims 1-4, 7-11, 13, 15, 19, and 25-30 have been considered but are moot in view of the new ground(s) of rejection.

9. The rejection of claims 1-10, 13, 25, and 28, and 25-30 under 35 USC § 102(b) as being anticipated by Gelfand et al. (1989) are withdrawn.

Although Applicant's argument concerning the pH range is are not found persuasive; Gelfand et al. do not meet the new limitation of claims 1, 5, 7, and 9 for a DNA polymerase fusion comprising wild type Pyrococcus furiosus polymerase I fused to Sulfolobus solfataricus SSso7d protein. Thus Gelfand et al. do not read on the amended claims and this rejection is withdrawn.

10. The rejection of claims 1-11, 26, 28, and 29 under 35 USC § 102(b) as being anticipated by Dahlberg et al. (1996) are withdrawn.

Applicant's argument concerning the pH range is are not found persuasive. Yet although Dahlberg et al. do teach a Pyrococcus furious polymerase; Dahlberg et al. do not meet the new limitation of claims 1, 5, 7, and 9 for a DNA polymerase fusion comprising Sulfolobus solfataricus SSso7d protein. Thus Dahlberg et al. do not read on the amended claims and this rejection is withdrawn.

New Rejections Necessitated by Amendment

Claim Rejections - 35 USC § 112

11. Claims 1-11, 13, 15, 19, and 25-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a range of pH 9.3 to 10, does not reasonably provide enablement for a range of pH 9.3 to 14. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The nature of the invention and breadth of claims

Base claims 1, 6, 7, and 9 recite synthesizing DNA with a protein fusion polymerase in the pH range of 9.3 to 14 . In fact the specification does not disclose that the fusion polymerase will operate above pH 10.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there the art teaches that protein hydrolyses at pH 10 and higher. Ernster (United States Patent 4,545,933 issued 1985) teaches that proteins are hydrolyzed at pH 10 and higher (see claims 9 and 19).

Working Examples

The specification has no working examples of synthesizing DNA in the pH range of 10 to 14 with a protein fusion polymerase.

Guidance in the Specification.

The specification provides no evidence that the disclosed protein fusion polymerase would be able to function in pH range of 10 to 14.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, given the broad claims in an art which teaches opposite of the claims, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written, if in fact, it were possible.

New Claim Rejections - 35 USC § 103

12. Claims 1-4, 7-11, 13, 15, 19, 25-30, and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang (WO 01/082501 published 2001), cited on the Information Disclosure Statement, IDS.

Regarding claims 1, 3, 25, 27, and 30, Wang teaches a method for cloning of a DNA synthesis product at high pH comprising:

a) providing a DNA polymerase fusion which is Pfu (wild type)-Sso7d (see p. 39, lines 13-16 for DNA polymerase fusion at high pH: "The reaction buffer for Pfu-Sso7d [fusion], Taq, and Sso7d-Taq was the above buffer [pH 8.8] . . ." and see Table 1 of this Office Action for sequence matching to wild type Pfu-protein Sso7d fusion); and

(b) contacting said fusion with a nucleic acid template, wherein said fusion permits DNA synthesis (see p. 39, line 6: "Lambda DNA (2.25 pM) was used as a PCR template").

c) inserting said synthesized DNA product into a cloning vector (see page lines "This nucleic acid can then be easily ligated into a vector containing a nucleic acid encoding the second domain and having the appropriate corresponding restriction sites").

Regarding claim 7, Wang teaches a method of linear or exponential PCR amplification at high pH for random mutagenesis comprising the steps of:

incubating a reaction mixture comprising a nucleic acid template, at least one PCR primers, and a DNA polymerase fusion under conditions which permit amplification of said nucleic acid template by said fusion to produce a mutated amplified product (for production of a mutated product see the teachings concerning Taq polymerase and fusion products prepared with it, see p. 10 lines 19-21: "However, because of the low fidelity of such [Taq] polymerases, products cloned from such amplifications are likely to contain introduced mutations", and p. 35 lines 7-9: "*Unlike Taq polymerase*, Pfu possesses a 3' to 5' exonuclease activity, allowing it to maintain high fidelity during DNA synthesis", *emphasis* by Examiner).

Regarding claim 9, Wang teaches a method of reverse transcriptase PCR at high pH comprising the steps of

incubating a reaction mixture comprising a nucleic acid template, at least one PCR primer, and a DNA polymerase fusion under conditions which permit amplification of said nucleic acid template by said fusion to produce an amplified product (see p. 29, lines 12 and 13: "Similar assay conditions can be employed to test for improved processivity when the catalytic domain is a reverse transcriptase . . . ").

Regarding claims 2, 4, 8, and 10, Wang teaches a method comprising a PCR enhancing factor and/or an additive (see p. 39 lines 11-15 for additives and enhancing factors: "Each reaction contained 40 unit/ml of polymerase . . . and 0.36 mM of each of the four dNTPs. The reaction buffer used for Pfu (from Stratagene) contained 20 mM Tris-HCl (pH 8.8), 2 mM $MgS0_4$, 10 mM KCl, 10 mM $(NH4)_2SO_4$, 0.1% Triton X-100, and 0.1 mg/ml BSA").

Regarding claims 11 and 19, Wang teaches a method where the DNA polymerase fusion has reduced DNA polymerization activity (see p. 36, Table II where: PL-ΔTaq has <5% activity at 63°C which is less than the 85% activity of Taq at 63°C).

Regarding claims 13 and 15, Wang teaches a method where DNA polymerase fusion comprises reduced base analog detection activity (see p. 20, line 25-26: "In addition, nonclassical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the sequence").

Regarding claims 26 and 28, Wang teaches a method where a DNA polymerase fusion is a proofreading polymerase (see p. 2, lines 9 and 10: "These modified enzymes, e.g., Pfu-Sso7d, incorporate a polymerase with 10 error-correcting activity . . . ", and p. 6 line 28 and 29: " 'Error-correcting activity' of a polymerase or polymerase domain refers to the 3' to 5' exonuclease proofreading activity of a template-specific nucleic acid polymerase . . .", and p. 38 lines 27 and 28: "As demonstrated in Example 2, Sso7d fusion proteins have significantly higher processivity than their unmodified counterparts").

Regarding claims 29, Wang teaches a method where a DNA polymerase fusion further comprises a polypeptide with a reduced extension time in a PCR reaction (see p. 2 lines 12-14: "In addition, such modified enzymes can efficiently amplify a given fragment using shorter extension times than are required by conventional polymerase mixtures").

Regarding claims 1, 3, 7, and 9 Wang does teach pH 8.8 but does not specifically teach the pH range of 9.3 to 10.

However, it would also have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use a pH in range of 9.3-10 as used by the applicant which is in the range of pH 8.8 as used by Wang, since these differences in pH would not be expected to greatly alter the conditions for amplification.

This is consistent with the Federal Circuit decision in In re Peterson, 65 USPQ2d 1379, 1382 (Fed. Cir. 2003) "We have also held that a prima facie case of obviousness exists when the claimed range and the prior art range do not overlap but are close enough such that one skilled in the art would have expected them to have the same properties." Thus, an ordinary practitioner would have recognized that a higher pH range would be a workable range with the DNA polymerase fusion maintaining activity.

As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the examination of pH was other than routine, that the products resulting

from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art. As noted, a skilled artisan would expect a DNA polymerase fusion which has activity at pH 8.8 to continue to have activity from pH 9.3 to 10 in the amplification of nucleic acids. Thus, an ordinary practitioner would have recognized that the pH could be adjusted to while still maintaining activity.

Regarding claim 40, Wang teaches a DNA polymerase fusion where the Pfu polymerase and the Sso 7d protein are encoded by SEQ ID NO: 126 and have amino acid sequences found in SEQ ID NO: 127 (see Table 1 of the Office Action mailed on 12/08/2006). Wang does not specifically teach the nucleic acid sequence and 18 amino acid sequence regions respectively of SEQ ID NO: 126 and SEQ ID NO: 127 linking the Pfu polymerase to the Sso 7d protein. However, Wang does teach: "The linker sequence may generally be from 1 to about 50 amino acids in length, e.g., 3,4,6, or 10 amino acids in length, but can be 100 or 200 amino acids in length" (see p. 21 lines 20-24).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the DNA polymerase fusion sequences by using an amino acid linker as suggested by Wang with a reasonable expectation of success. The motivation to do so is provided by Wang who teach: "The means of linking the heterologous domains of the protein may also comprise a peptidyl bond formed between moieties that are separately synthesized by standard peptide synthesis

chemistry or recombinant means"(see p. 20 lines 10-12). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Objections and Rejections that are Maintained

13. The improper use of trademark DEEP VENT™ is maintained as this trademark needs to capitalized.

Claim Rejections Maintained - 35 USC § 103

14. The rejection of claims 5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang (2001) as applied to claims 1-4, 7-11, 13, 15, 19, and 25-30 above, and further in view of Sanger et al. (1977) is maintained.

Applicant's arguments filed on 06/08/2007 have been fully considered but they are not persuasive. On pages 18, Applicant argues that the newly amended claim limitation of a pH range of 9.3-10 is not met in the teachings Sanger et al. However as noted above Sanger et al. is not relied upon for this limitation, Wang is. Therefore, the rejections are maintained.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

16. No claim is free of the prior art.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mark Staples
Examiner
Art Unit 1637
August 14, 2007

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER
8/15/07